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Evidence-Based Evaluation of Calcium Channel Blockers for Hypertension

Equality of Mortality and Cardiovascular Risk Relative to Conventional Therapy

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OBJECTIVES We present a meta-analysis based on three recent, substantial, randomized outcome trials and several smaller trials that compared calcium channel blockers (CCBs) with conventional therapy (diuretics or beta-blockers) or with angiotensin-converting enzyme (ACE) inhibitors

BACKGROUND There is continuing uncertainty about the safety and efficacy of CCBs in the treatment of hypertension. Previous meta-analyses conflict and suggest that CCBs increase myocardial infarction (MI) or protect from stroke.

METHODS Standard procedures for meta-analysis were used to analyze three major trials on 21,611 patients and another three lesser studies to a total of 24,322 patients.

RESULTS Calcium channel blockers have a strikingly similar risk of total and cardiovascular mortality and of major cardiovascular events to conventional therapy. Calcium channel blockers give a lower risk of nonfatal stroke (−25%, p = 0.001) and a higher risk of total MI (18%, p = 0.013), chiefly nonfatal (18%). After performing the Bonferroni correction for multiplicity, these p values become 0.004 and 0.052, respectively. When compared with ACE inhibitors in 1,318 diabetic patients, CCBs had a substantially higher risk of nonfatal (relative risk [RR] = 2.259) and total MI (RR = 2.204, confidence interval 1.501 to 3.238; p = 0.001 or 0.004 with Bonferroni correction). Total and cardiovascular mortality rates are similar. To confirm the hypothesis that ACE inhibitors are superior to CCBs in diabetic patients requires more trial data, especially with renal end points.

CONCLUSIONS Mortality (total and cardiovascular) and major cardiovascular events with CCBs were apparently similar to those events seen with conventional first-line therapy (diuretics or beta-blockers). Stroke reduction more than balanced increased MI. In diabetics, CCBs may be less safe than ACE inhibitors. (J Am Coll Cardiol 2002;39:315–22) © 2002 by the American College of Cardiology

Considerable evidence points to the cardiovascular harm of short-acting dihydropyridines, such as capsular nifedipine, although several studies suggest that longer acting calcium channel blockers (CCBs) may have fewer or possibly no adverse effects (1,2). Nonetheless, the safety of longer acting CCBs in the long-term treatment of hypertension has remained an open issue. The recent reporting of three large, well designed, randomized, controlled trials (3–5) requires a fresh assessment of the safety and efficacy of CCBs in hypertension. These and other studies have given rise to two important recent meta-analyses (6,7). Furberg's group (6) concluded that CCBs as initial antihypertensive therapy increased myocardial infarction (MI) by 26%, whereas the Blood Pressure Trialists (7) concluded that there was a significant decrease in stroke with CCBs, with only a borderline increase in MI. Because both groups found that CCBs and conventional therapy had indistinguishable effects on mortality (total and cardiovascular), we reasoned that a consideration of nonfatal events might help explain the discrepancies. We have separately compared CCB-based therapy with "conventional therapy," initially with diuretics or beta-blockers and thereafter with angiotensin-converting enzyme (ACE) inhibitors. There are two reasons for the separate comparisons. First, an influential U.S. document suggests that such conventional treatment should be the first-line antihypertensive therapy, with ACE inhibitors selected only for specific subgroups (8). Thus, it is crucial to know how CCBs compare with conventional therapy. Second, ACE inhibitors may have cardioprotective properties beyond blood pressure control (9,10). In contrast to both the Blood Pressure Trialists (7) and Furberg group (6), we also assessed diabetic patients separately from others, in view of the well-known increase of cardiovascular risk in diabetics. In addition, in contrast to both studies, we graded the quality of the studies in our meta-analysis, and only the three major studies received grade A (Table 1). We have also considered three lesser trials to which we assigned a grade B status (11–15) and one trial that we excluded (see Methods). These comparisons point the way toward evidence-based and outcome-related comparisons of the

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Abbreviations and Acronyms

ABCD	= Appropriate Blood pressure Control in Diabetes trial
ACE	= angiotensin-converting enzyme
CASTEL	= Cardiovascular Study of the Elderly
CCB	= calcium channel blocker
CI	= confidence interval
FACET	= Fosinopril versus Amlodipine Cardiovascular Events Trial
MI	= myocardial infarction
MIDAS	= Multicenter Isradipine Diuretic Atherosclerosis Study
RR	= relative risk
STOP-Hypertension	= Swedish Trial in Old Patients with Hypertension

efficacy and safety of CCBs and other groups of antihypertensive agents. Our results also allow explanation of the two apparently conflicting meta-analyses by Furberg's group (6) and the Blood Pressure Trialists (7).

METHODS

The major part of the study concerns the comparison between initial therapy with CCBs and conventional therapy, where the latter is defined as initial therapy with either a diuretic or beta-blocker, but not both. To gather all eligible trials of hypertension, we conducted a continuous search of the published data over five years (1,16), and we cross-checked our trial inclusions with those of Furberg's group (6). Ideally, the trials had to satisfy six criteria (translated into points): 1) randomization; 2) blinded fashion or with the Prospective, Randomized, Open, Blinded End point evaluation design, as in the Swedish Trial in Old Patients with Hypertension-2 (STOP-Hypertension-2) (4) and Nordic Diltiazem study (5); 3) clearly and prospectively predefined clinical end points, such as mortality, stroke, heart failure and MI; 4) inclusion of >1,000 patients, to give reliable numbers of outcome measures; 5) use of medium- or long-acting CCBs, but not with short-acting CCBs, which are known to increase cardiovascular end points; and 6) duration of ≥2 years. As pointed out by Flather et al. (17), most of the clinically useful information comes from the large randomized trials of ≥1,000 patients. Six trials involving conventional therapy satisfied three or more of these criteria. Trials that satisfied at least 5 of those 6 points were assigned a grade A status (Table 1). Grade B trials satisfied only ≤4 points.

The sum of events due to MI, stroke and heart failure was taken as major cardiovascular events, and the sum of deaths caused by these events was the total cardiovascular mortality (Tables 2 and 3).

As an example of the grading system, the National Intervention Cooperative Study in Elderly Hypertensives study (11) was graded as B because of the small number of patients and because the clinical end points were not predefined. The Verapamil in Hypertension Atherosclerosis Study (12) was graded as B, because the cardiovascular end points were a secondary aim and were not clearly predefined, and the trial was largely open-label. The Multicenter Isradipine Diuretic Atherosclerosis Study (MIDAS) (13) received the lowest grade B rating, because it used a short-acting dihydropyridine that is known to increase cardiovascular risk (1,18). The primary end points did not include clinical outcomes, nor were these predefined.

The Cardiovascular Study of the Elderly (CASTEL), although included by Furberg's group (6), was excluded because of a fundamental trial defect: CASTEL compared an inadequate dose of nifedipine retard tablets, which need to be given twice a day, but were only given once a day with dual therapy with two long-acting agents: high-dose atenolol and a diuretic agent (19). Thus, comparable 24-h blood pressure control in the two groups could not have been achieved. Furthermore, CASTEL was seriously imbalanced, with 24% diabetic patients in the nifedipine-treated group and 13% in the other group. The Blood Pressure Trialists (7) omitted both CASTEL and the Fosinopril versus Amlodipine Cardiovascular Events Trial (FACET) (15) from their prospective meta-analysis.

The second part of the study compares initial CCB therapy with ACE inhibitor therapy (Table 3). Here, there was only one satisfactory study—STOP-Hypertension-2 (4). The STOP-Hypertension-2 diabetic substudy of 719 patients was classified as grade A, lacking only the sample size criterion (20). Appropriate Blood pressure Control in Diabetes (ABCD) is a difficult trial to assess, because it was terminated prematurely, and especially because the outcomes in the final report differed substantially from those already published (14). Therefore, although it was randomized and double-blinded, ABCD was assigned to grade B. The FACET was graded as B; it was open-labeled, the primary and secondary end points were not clearly defined, some data were lacking and the clinical events were analyzed retrospectively.

A joint analysis of grade A trials is presented. Furthermore, to assess the sensitivity of the results to the entry criteria for the meta-analysis, a joint analysis of grade A and B trials is also presented. To further assess the sensitivity, there is also an analysis excluding MIDAS, which has the lowest number of points in grade B (Table 1). Combined estimates of relative risk (RR), with 95% confidence intervals (CIs), across studies were calculated by the Mantel-Haenszel method, with "trial" as the stratification factor. Combined p values were obtained by the Cochran-Mantel-Haenszel chi-square test, but p values for individual studies were obtained from the Fisher exact test. The homogeneity of the odds ratio across trials was tested using the Breslow-Day test. The Bonferroni correction was used to assess the possible effect of multiple comparisons (21). We reasoned that the four primary events in the trials were nonfatal and fatal stroke and nonfatal and fatal MI, with other events

Table 1. Entry Criteria as Met by Trials Comparing Calcium Channel Blockers With Conventional Therapy

Criterion	INSIGHT (Ref. 3)	STOP-Hypertension-2 (Ref. 4)	NORDIL (Ref. 5)	NICS-EH (Ref. 11)	VHAS (Ref. 12)	MIDAS (Ref. 13)
Randomized	+1 CCB vs. diuretic	+1 CCB vs. diuretic or beta-blocker	+1 CCB vs. diuretic or beta-blocker	+1 CCB vs. diuretic	+1 CCB vs. diuretic	+1 CCB vs. diuretic
Double-blinded or PROBE design*	+1 Double-blinded	+1 PROBE	+1 PROBE	+1 Double-blinded	+0 Double-blinded; then open-label	+1 Double-blinded; 3 years
Predefined clinical end points; primary end points	+1 Total CV morbidity	+1 Fatal CV disease	+1 Stroke, MI, all CV deaths	+0 CV events	+0 Not given	+0 Not given
Not short-acting CCB; specific drug used	+1 nifedipine GITS	+1 felodipine or isradipine	+0 diltiazem, initially short-acting	+1 nicardipine	+1 verapamil, slow release	+0 isradipine, short-acting
Large trial (>1,000) Total number	+1 6,321	+1 6,614	+1 10,881	+0 414	+1 1,414	+0
Duration ≥2 years	+1 (at least 3 years)	+1 (up to 6 years)	+1 (up to 5 years)	+1 5 years	+1 2 years	+1
Total points	6	6	5	4	4	3

*PROBE = Prospective, Randomized, Open, Blinded Endpoint evaluation design; see test for details.
CCB = calcium channel blocker; CV = cardiovascular; GITS = gastro-intestinal tract system; MI = myocardial infarction; trial acronyms are defined in the references.

Table 2. Stroke: Calcium Channel Blocker-Based Therapy Versus Conventional Therapy of Hypertension

	CCB (n/N)	CT (n/N)	RR*	95% CI	p Value	Heterogeneity†
Stroke, nonfatal						
INSIGHT (ref. 3)	55/3,157	63/3,164	0.875	0.611–1.252	0.516	
NORDIL (ref. 5)	138/5,410	174/5,471	0.802	0.644–1.000	0.051	
STOP-2 (ref. 4)	120/2,196	186/2,213	0.650	0.521–0.812	<0.001	
Total, grade A	313/10,763	423/10,848	0.746	0.647–0.860	0.001	0.227
VHAS (ref. 12)	3/707	4/707	0.750	0.168–3.339	1.000	
NICS-EH (ref. 11)	8/204	8/210	1.029	0.394–2.691	1.000	
MIDAS (ref. 13)	No data	No data	No data	No data	No data	
Total of above	324/11,674	435/11,765	0.751	0.653—0.864	0.001	0.495
Stroke, fatal						
INSIGHT	12/3,157	11/3,164	1.093	0.483–2.474	0.838	
NORDIL	21/5,410	22/5,471	0.965	0.531–1.753	1.000	
STOP-2	207/2,196	237/2,213	0.880	0.737–1.050	0.161	
Total, grade A	240/10,763	270/10,848	0.896	0.759–1.058	0.194	0.829
VHAS	3/707	0/707	‡	‡	0.249	
NICS-EH	3/204	0/210	‡	‡	0.119	
MIDAS	No data	No data	No data	No data	No data	
Total of above	246/11,674	270/11,765	0.918	0.779–1.083	0.311	0.127
Total stroke						
INSIGHT	67/3,157	74/3,164	0.907	0.654–1.258	0.610	
NORDIL	159/5,410	196/5,471	0.820	0.668–1.008	0.059	
STOP-2	207/2,196	237/2,213	0.880	0.737–1.050	0.161	
Total, grade A	433/10,763	507/10,848	0.861	0.761–0.975	0.018	0.849
VHAS	3/707	4/707	0.750	0.168–3.339	1.000	
NICS-EH	8/204	8/210	1.029	0.394–2.691	1.000	
Total grades A and B	450/12,116	522/12,206	0.869	0.769–0.982	0.024	0.849

*RR = relative risk of calcium channel blocker (CCB) therapy versus conventional therapy (CT); CI = confidence interval. †The Breslow-Day test was used for heterogeneity; ‡Statistics were not calculated for empty cells.
Trial acronyms are defined in the references.

such as heart failure and mortality not independent of these four.

RESULTS

Comparisons of CCBs with conventional therapy. In grade A studies with 21,611 subjects, total mortality (RR 1.005, CI 0.914 to 1.105) and cardiovascular mortality were indistinguishable for the two modes of therapy (CCBs vs. conventional therapy), as was the risk of major cardiovascular events (Tables 2 and 3, Fig. 1). The risk of nonfatal stroke for CCBs compared with conventional therapy was 25% lower ($p = 0.001$), and the risk of MI, chiefly nonfatal, was 19% higher ($p = 0.011$). The risk of heart failure was indistinguishable, although there was a trend against the CCBs. Adding in the grade B studies yielded a total of 24,322 subjects, again with indistinguishable total and cardiovascular mortality, a lower risk of nonfatal stroke (25%, $p = 0.001$) and a higher risk of MI (18%, $p = 0.013$), chiefly nonfatal (18%, $p = 0.036$) for CCBs compared with conventional therapy. Note that all of these p values are not necessarily significant, albeit $p < 0.05$. When using the Bonferroni correction for the four basic events covered in our analyses, these p values increased to 0.004, 0.044, 0.004, 0.052 and 0.144, respectively. Thus, the most statistically robust finding was related to a reduction of nonfatal stoke by CCBs. The overall findings are unchanged by omitting MIDAS (13), the weakest of the grade B studies.

Comparisons of CCBs with ACE inhibitors. There was only one grade A study—STOP-Hypertension-2 (4). This study showed differences favoring ACE inhibition that become insignificant with the Bonferroni correction. Combining three studies with a total of 1,318 diabetic hypertensive patients—namely, the STOP-Hypertension-2 diabetic study with the corrected ABCD data (used herein) and the small, open-label, data-deficient FACET (15)—accentuated the differences in favor of ACE inhibition (Table 4, Fig. 2). Thus, in diabetics, CCBs are related to a substantially higher risk of nonfatal (RR 2.259) and total MI (RR 2.204, CI 1.501 to 3.238; $p = 0.001$ or 0.004 with Bonferroni correction). Nonetheless, CCBs and ACE inhibitors have similar rates of total and cardiovascular mortality. This can be explained by the increased the risk of nonfatal, but not fatal, MI with the use of CCBs.

Homogeneity of data across studies. P values for the Breslow-Day test were >0.05. For the major events (total and cardiovascular mortality and major cardiovascular events), $p \geq 0.49$, except in the smaller diabetic trials.

DISCUSSION

Our major conclusion is that, over the periods of study, CCBs appear to be safe and effective when compared with conventional therapy, defined as initiation of therapy with either a diuretic or beta-blocker. The risks of total and cardiovascular mortality, as well as major cardiovascular

Table 3. Myocardial Infarction, Heart Failure and Major Cardiovascular Events: Calcium Channel Blocker-Based Therapy Versus Conventional Therapy of Hypertension

	CCB (n/N)	CT (n/N)	RR*	95% CI	p Value	Heterogeneity†
MI, nonfatal						
INSIGHT (ref. 3)	61/3,157	56/3,164	1.092	0.762–1.564	0.642	
NORDIL (ref. 5)	155/5,410	132/5,471	1.187	0.944–1.493	0.151	
STOP-2 (ref. 4)	120/2,196	99/2,213	1.222	0.942–1.583	0.145	
Total grade A	336/10,763	287/10,848	1.180	1.011–1.378	0.036	(0.872)
VHAS (ref. 12)	5/707	5/707	1.000	0.291–3.439	1.000	
NICS-EH (ref. 11)	2/204	2/210	1.029	0.146–7.239	1.000	
MIDAS (ref. 13)	6/442	5/441	1.197	0.368–3.894	1.000	
Total grades A and B	349/12,116	299/12,206	1.177	1.011–1.370	0.036	(0.996)
MI, fatal						
INSIGHT	16/3,157	5/3164	3.207	1.176–8.744	0.017	
NORDIL	28/5,410	25/5471	1.133	0.661–1.940	0.681	
STOP-2	59/2,196	55/2213	1.081	0.752–1.553	0.705	
Total grade A	103/10,763	85/10848	1.222	0.919–1.623	0.168	(0.115)
VHAS	3/707	4/707	0.750	0.168–3.339	1.000	
NICS-EH	0/204	0/210	—	—	‡	
MIDAS	—	—	—	—	‡	
Total grades A and B	106/11,674	89/11,765	1.200	0.908–1.587	0.200	(0.193)
MI, total						
INSIGHT	77/3,157	61/3,164	1.265	0.907–1.764	0.169	
NORDIL	183/5,410	157/5,471	1.179	0.956–1.454	0.137	
STOP-2	179/2,196	154/2,213	1.171	0.952–1.441	0.139	
Total grade A	439/10,763	372/10,848	1.190	1.040–1.361	0.011	(0.935)
VHAS	8/707	9/707	0.889	0.345–2.291	1.000	
NICS-EH	2/204	2/210	1.029	0.146–7.239	1.000	
MIDAS	6/442	5/441	1.197	0.368–3.894	1.000	
Total grades A and B	455/12,116	388/12,206	1.182	1.036–1.349	0.013	(0.991)
Heart failure						
Total grades A and B	279/12,116	245/12,206	1.148	0.972–1.356	0.104	(0.054)
Major CV events						
Total grades A and B	1,261/12,116	1257/12,206	1.011	0.940–1.087	0.767	(0.749)
Total CV mortality						
Total grades A and B	411/12,116	395/12,206	1.049	0.917–1.199	0.486	(0.805)

*RR = relative risk of calcium channel blocker (CCB) therapy versus conventional therapy (CT); CI = confidence interval. †The Breslow-Day test was used for heterogeneity; ‡Statistics were not calculated for empty cells.
(—) = absence of data; CV = cardiovascular; MI = myocardial infarction; trial acronyms are defined in the references.

outcomes, were apparently indistinguishable when comparing CCBs and conventional therapy (Tables 2 and 3). Conventional therapy, as compared with placebo, is known to reduce mortality in elderly hypertensive patients (22).

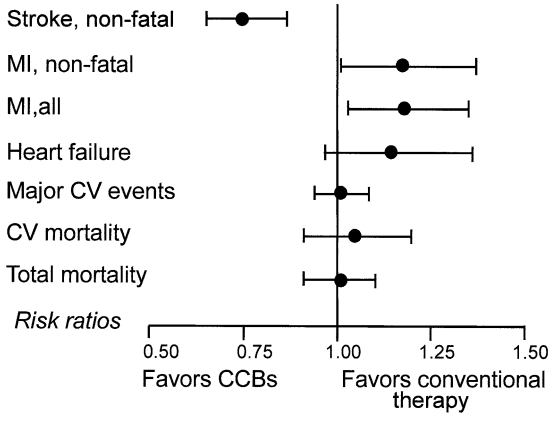

Figure 1. Comparison between calcium channel blocker (CCB) based therapy and conventional therapy. For details, see Tables 2 and 3. Note the decrease (p = 0.001) in nonfatal stroke and the increase in nonfatal myocardial infarction (MI) (p = 0.036). CV = cardiovascular.

Two placebo-controlled trials of CCB-based therapy also showed reduced total mortality (23,24). Therefore, it is reasonable to deduce that CCB-based therapy, as compared with placebo, for hypertension potentially reduces all-cause mortality, depending on the patient's risk profile.

Quality of the meta-analysis. The quality of any meta-analysis, including ours, partly depends on the combinability of the information provided by the trials, the quality of the trial designs and the carefulness of the clinical data collection. These requirements were not all satisfactorily met in the various studies, which led us to use a grading system in the present meta-analysis. Of note, even the grade A studies differ with respect to clinical factors such as patient age and final blood pressure achieved. The mortality rate in STOP-Hypertension-2 (4) was 16.7%, but <5% in the other two grade A trials (3,5). However, although the absolute risk levels vary considerably across studies, the RRs for total and cardiovascular mortality, major cardiovascular events, stroke, nonfatal MI and all MIs are homogeneous across the studies (see the p values for Breslow-Day test). This justifies combining the estimates of RR across the studies and

Table 4. Diabetic Hypertensive Therapy Based on Calcium Channel Blockers and Angiotensin-Converting Enzyme Inhibitors

	CCB (n/N)	ACE Inhibitors (n/N)	RR*	95% CI	p Value	Heterogeneity†
Stroke						
STOP-2, nondiabetic (ref. 4)	178/1,965	181/1,968	0.985	0.809–1.200	0.912	
STOP-2, diabetic, grade A (ref. 20)	29/231	34/237	0.875	0.552–1.388	0.591	
ABCD, diabetic, grade B (ref. 14)	11/235	7/235	1.571	0.620–3.984	0.472	
FACET, diabetic, grade B (ref. 15)	10/191	4/189	2.474	0.790–7.750	0.172	
Total diabetic	50/657	45/661	1.129	0.770–1.654	0.535	(0.176)
MI, nonfatal						
STOP-2, nondiabetic	52/1,965	44/1,968	1.184	0.796–1.760	0.411	
STOP-2, diabetic, grade A	25/231	13/237	1.973	1.035–3.761	0.042	
ABCD, diabetic, grade B	24/235	9/235	2.667	1.267–5.614	0.010	
Total diabetic	49/466	22/472	2.259	1.410–3.618	0.001	(0.561)
MI, fatal						
STOP-2, nondiabetic	52/1,965	44/1,968	1.184	0.796–1.760	0.411	
STOP-2, diabetic, grade A	7/231	4/237	1.795	0.533–6.051	0.377	
ABCD, diabetic, grade B	3/235	0/235	—	‡	0.248	
Total diabetic	10/466	4/472	2.555	0.842–7.755	0.098	(0.223)
MI, all						
STOP-2, nondiabetic	147/1,965	122/1,968	1.207	0.957–1.522	0.115	
ABCD, diabetic, grade B	27/235	9/235	3.000	1.442–6.240	<0.001	
FACET, diabetic, grade B	13/191	7/189	1.838	0.750–4.505	0.250	
STOP-2, diabetic, grade A	32/231	17/237	1.931	1.104–3.380	0.023	
Total diabetic	72/657	33/661	2.204	1.501–3.238	0.001	(0.597)
Heart failure						
STOP-2, nondiabetic	162/1,965	127/1,968	1.278	1.021–1.598	0.032	
STOP-2, diabetic, grade A	24/231	22/237	1.119	0.646–1.939	0.757	
ABCD, diabetic, grade B	8/235	10/235	0.800	0.321–1.991	0.811	
Total diabetic	32/466	32/472	1.019	0.637–1.630	0.939	(0.534)
Major CV events	115/466	93/472	1.258	0.992–1.595	0.059	(0.075)

*RR = relative risk of calcium channel blocker (CCB) therapy versus conventional therapy (CT); CI = confidence interval. †The Breslow-Day test was used for heterogeneity; ‡Statistics were not calculated for empty cells.

(—) = absence of data; ACE = angiotensin-converting enzyme; CV = cardiovascular; MI = myocardial infarction; trial acronyms are defined in the references.

suggests that the relative efficacy and safety of CCBs may withstand the differences in clinical factors between the trials included in this analysis. Furthermore, by using our grading system, we could show that inclusion of grade B trials in the meta-analysis, a procedure that constitutes a limited sensitivity analysis, did not materially affect the results. This suggests a certain robustness of our findings in relation to the inclusion criteria for the trials in this meta-analysis. Of note, neither the other investigators nor we (6,7) used funnel plots in the meta-analyses presented, because of the relatively small number of trials.

All meta-analyses may suffer from inclusion and exclusion bias (25) and from the inherent statistical weakness of the data included. We have attempted to avoid bias by analyzing all of the trials cited by Furberg's group (6) and by using our grading system, as well as by giving full reasons for rejection of one study. Meta-analyses, which by nature involve multiple comparisons, may require a very low p value, possibly as low as 0.001, to reach significance with confidence (26). This value was reached for the CCB effect on nonfatal stroke (Table 2). We also provide Bonferroni corrections in an attempt to compensate for the inevitable multiple comparisons made in our analyses. In addition, each trial had multiple outcomes. For these reasons, relatively small differences between CCB and conventional therapy should be regarded with reserve, whereas the lack of

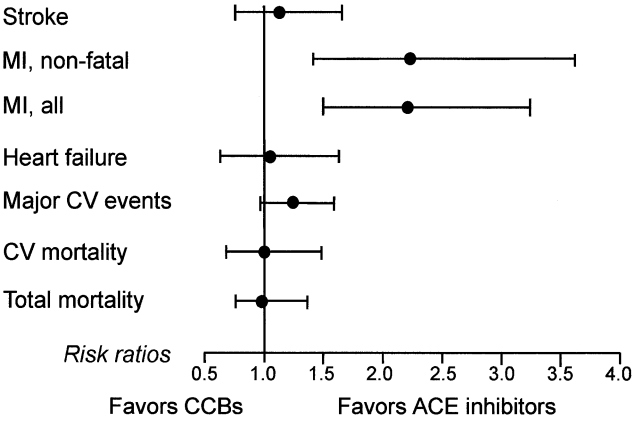

Figure 2. Comparison between calcium channel blocker (CCB) based therapy and angiotensin-converting enzyme (ACE) inhibitor-based therapy. For details, see Table 4. Note the increase in nonfatal and total myocardial infarction (MI). CV = cardiovascular.

difference in relation to the major outcomes, such as cardiovascular mortality and major events, is striking. However, we cannot exclude that with larger numbers, some of the trends, such as those in heart failure, might show adverse effects for CCBs, in keeping with the CIs (Fig. 1), which, in turn, would influence major cardiovascular events.

Hypertension in diabetics. When compared with ACE inhibitors in diabetic hypertensive patients, CCBs have an apparently indistinguishable effect on total and cardiovascular mortality, stroke and heart failure (Table 4). However, CCBs have a substantially higher risk of nonfatal (RR 2.259) and total MI (RR 2.204, CI 1.501 to 3.238; $p = 0.001$ or 0.004 with Bonferroni correction). In nondiabetics, these changes did not reach significance. However, these conclusions must still be viewed with caution. Subgroup analysis, even with multiplicity correction, is only justified if the overall trial shows little benefit (as for mortality in this meta-analysis) and if the hypothesis regarding subgroup effects has a strong biologic rationale (26). We tested the hypothesis that ACE inhibitors are superior to CCBs in hypertensive diabetic patients. However, STOP-Hypertension-2 is the only grade A study based on the comparison of CCBs and ACE inhibitors (4). Furthermore, the total number of diabetic hypertensive patients (n = 1,318) and trials (n = 3) comparing CCBs and ACE inhibitors is much less than that in comparisons between CCBs and conventional therapy (n = 24,322 and 6 trials), giving much greater credence to the conclusions derived from the latter comparison. Regarding diabetic nephropathy, a recent study (27) shows that inhibition of the renin-angiotensin system by irbesartan is superior to amlodipine in renal end point reduction, yet amlodipine reduced MI by 41%.

Our data help to interpret the apparently conflicting conclusions of the two previous meta-analyses. Furberg's group did not mention in their abstract or discussion that comparing CCBs with conventional therapy gave a small reduction in stroke (14%) and a small increase in heart failure (20%) and MI (22%), with p values (<0.05) that would lose significance when Bonferroni-corrected (6). In contrast, when comparing CCBs with ACE inhibitors, MI was increased (43%), with a very low p value ($p = 0.001$). We suggest that it is the inclusion of the ACE inhibitor data, together with data on conventional therapy, that skews the overall Furberg meta-analysis toward inferiority of the CCBs. Like us, the Blood Pressure Trialists separated the comparison of CCBs with conventional therapy from that with ACE inhibitors and found virtual equality with conventional therapy. The Blood Pressure Trialists could find no clear evidence of differences between ACE inhibitors and CCBs (7), even though ACE inhibitors appear to have strong protective effects, when compared with placebo, in high-risk diabetic patients (10). However, they did not have data on the diabetic subgroup of STOP-Hypertension-2. These are the data that, together with the lower grade B studies previously available (i.e., ABCD and FACET), argue for the inferiority of CCBs versus ACE inhibition in diabetic patients. Of note, Furberg's group included two diabetic studies and the Blood Pressure Trialists included only one, whereas we separately considered three diabetic studies. Yet the diabetic database remains small. Additional data from currently running, well-designed trials, such as the Antihypertensive and Lipid Lowering treatment to prevent Heart Attack Trial, are required to confirm the superiority of ACE inhibitors in hypertensive diabetic patients.

Study limitations. There are several limitations of our study. First, we collected data retrospectively. Likewise, this is a defect of the Furberg study (6), although not of the Blood Pressure Trialists' study, which was prospective (7). A second defect of our study, and of both the others, is the substantial number of statistical tests undertaken, with many subgroups, to give the primary data. The limits of statistical significance are difficult to define with precision. However, we did use the Bonferroni correction, which neither of the other studies did, despite their analyses of numerous subgroups. We have shown that several of the differences noted in the other two studies (6,7) became insignificant when thus corrected. Third, none of the studies relate the comparisons between CCBs and ACE inhibitors to renal outcomes in hypertensive patients. In the African American Study of Kidney Disease and Hypertension of African Americans with hypertensive renal disease, the amlodipine arm was withdrawn because of worse renal outcomes at equal blood pressure reductions, whereas the ramipril arm continued (28). Thus, in situations where there is a high risk of renal involvement (e.g., diabetics, African Americans), there is emerging evidence that dihydropyridines are inferior to inhibition of the renin-angiotensin system. Fourth, and most importantly, controlled trials are time-limited by their nature, whereas antihypertensive therapy is often life-long. Very long-term data may yet emerge from carefully designed, prospective, observational data.

Conclusions. We propose that CCBs are safe in the therapy of hypertension over the periods tested, with risks of mortality (total and cardiovascular) and major cardiovascular events apparently similar to those of conventional first-line therapy with diuretics or beta-blockers. However, in diabetic hypertensive patients, ACE inhibition may give superior cardiovascular protection, specifically against nonfatal MI. This proposal, although based on a statistically robust difference, is only provisional, because of the limited database. Further comparative data are required.

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